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New Drugs in the Management of the Irritable Bowel Syndrome

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Contents

Abstract

Irritable bowel syndrome (IBS) continues to provide a major therapeutic challenge to clinicians and those involved in drug development. It seems unlikely from the data before us that this multisymptom syndrome with peripheral and central components is likely to respond reliably in all patients to the same single agent. There is still a lack of well designed, appropriately powered, randomised clinical trials and the problems of dealing with the high placebo response rate in this group of patients remains a dilemma for trial designers.

There are, however, some new ideas, particularly those relating to the role of hyperalgesia in IBS. For many patients, abdominal pain and bloating are the most distressing symptoms of this disease and the new drugs targeted at pain control, such as κ agonists and serotonin antagonists (5-HT_3 and possibly 5-HT_4), may eventually find a place in the clinical management of this syndrome. Other candidates include somatostatin analogues and antidepressants, the latter predominantly for their effects on increasing pain threshold. More speculative new drugs for IBS include cholecystokinin antagonists such as loxiglumide and the gonadotrophin-releasing hormone analogue, leuprorelin (leuprolide). The results of ongoing randomised clinical trials are still awaited for some of these newer agents.

The irritable bowel syndrome (IBS) is the most common gastrointestinal condition encountered by general practitioners and is reported to account for up to 50% of the work of gastroenterologists in secondary care.[1] However, most people with the symptoms of IBS (60 to 75%) do not consult a doctor. Its cause is unknown, its development is poorly understood and, perhaps not surprisingly, no universally agreed approach to treatment exists.

1. Overview

1.1 The Therapeutic Challenge

As correctly identified by its name, IBS is a syndrome, a consortium of symptoms which is considered by some to be related to a broader spectrum of functional abdominal disorders from the oesophagus to the anorectum.[1] The retarded development of robust therapeutic strategies to treat IBS relates to a number of factors including its poorly defined pathophysiology, the high placebo response rate of patients with IBS (about 70%) and the observation that, in addition to the now well defined abdominal symptoms associated with IBS, there are often accompanying symptoms in other parts of the body (urinary symptoms, dyspareunia, fatigue). In addition, 40 to 60% of patients who seek medical advice have psychological symptoms of depression and anxiety or both.[1] The therapeutic challenge, therefore, is substantial and, at this point in our understanding of the disorder, it seems unlikely that a single medication can reliably treat this consortium of symptoms.

This is supported by the literature review by Klein[2] who concluded that the majority of clinical trials of therapeutic agents in IBS were flawed; none of the agents considered in his review could be regarded as effective in the treatment of IBS. Since this review, the definitions of IBS have been refined and entry criteria for randomised control trials have been tighter, although many of the more recent studies remain suboptimal because of the absence of placebo controls and lack of power in their study design.

1.2 Definition

Manning et al.[3] described a number of abdominal symptoms that were more likely to be present in IBS than in organic abdominal disease (table I). These symptoms have been tested prospectively in subsequent studies and their validity confirmed. More recently, a group of experts reconsidered the diagnostic criteria for IBS and refined the definition to what is now commonly known as the Rome Criteria[4] (table II). The Rome Criteria are now frequently used as entry criteria for clinical studies and randomised controlled trials in IBS.

1.3 Epidemiology

IBS affects up to 20% of adults in the industrialised world although the condition is not limited to Western countries, with similar prevalence data being reported from India, Japan, South America and China; prevalence may be lower in other parts of South-East Asia and in Africa.[1] Although it is commonly believed that the condition is more frequent in women, community-based studies suggest that IBS symptoms are found equally in men and women but women more commonly seek medical advice about their symptoms. Individuals with IBS frequently have other manifestations of the disease, which appear to be associated with their IBS symptoms, the so-called noncolonic symptoms of IBS.[5] These include urinary symptoms such as frequency and nocturia, dyspareunia, back pain and fatigue. In addition, IBS symptoms sometimes overlap with other functional abdominal disorders such as nonulcer dyspepsia and oesophageal symptoms. In addition, 40 to 60% of patients who seek medical advice have depression or anxiety or a combination

Table I. Symptoms found more commonly in irritable bowel syndrome than in organic abdominal disease[3]

Pain eased after bowel movement
Looser stools at onset of pain
More frequent bowel movements at onset of pain
Abdominal distension
Mucus in rectum
Feeling of incomplete emptying

Table II. Diagnostic criteria for irritable bowel syndrome[4]

At least 3mo of continuous or recurrent symptoms of
abdominal pain or discomfort which is
relieved with defecation *and/or*
associated with change in frequency of stool *and/or*
associated with a change in stool consistency
2 or more of the following on at least a quarter of occasions or days
altered bowel frequency (>3 bowel movements a day or <3 bowel movements a week)
altered form of stool (lumpy/hard or loose watery stool)
altered passage of stool (straining, urgency or feeling of incomplete evacuation)
passage of mucus
bloating or feeling of abdominal distension

of the two. These patients also have attitudes to illness that make them more likely to be preoccupied by bodily symptoms and to attribute a serious organic cause to a symptom.[6-8]

1.4 Pathophysiology and Pathogenesis

There is no single pathophysiological marker of IBS.[9] This is perhaps not surprising in view of the broad spectrum of symptoms that can be encountered in this condition, and their various combinations. The variation in defecatory patterns, ranging from marked bowel frequency to constipation, suggests a motility disorder. Rapid bowel transit has been demonstrated in diarrhoea-predominant IBS which in some individuals is accompanied by manometric abnormalities. The converse may be found in constipation-predominant IBS. However, in most studies reporting these abnormalities, a proportion of IBS patients have results similar to those of healthy volunteers. Thus, although apparent abnormalities of motility in the small intestine and the colon have been identified, many inconsistencies exist and it is difficult to invoke a hypothesis that suggests that the IBS is due to a primary motor disorder of the gut.

The dominance of abdominal pain as a key symptom in the syndrome has led to the hypothesis that IBS, at least in part, is a disorder of gut sensation.[10] It has been debated as to whether the cause of IBS is merely increased awareness of normal gastrointestinal events, or whether there is a reduced sensation threshold for pathophysiological events. There is increasing evidence that sensitivity to balloon distension of the rectum and other parts of the gastrointestinal tract is increased in some IBS patients;[11] this is not due to a reduction of global pain threshold since somatic pain thresholds are either similar or increased compared with healthy volunteers.[12] Again, there are inconsistencies in the literature on gut sensation in IBS, although like the motility disturbances, alteration in visceral sensation remains an attractive therapeutic target.

The strong link between affective disorders and IBS in patients who seek medical advice suggests that there may be a central component to the syndrome. This concept is supported by the finding that IBS patients do not always have gut-centred symptoms but may have a more generalised alteration in smooth muscle activity and heightened visceral sensation such as appears to occur in the urinary bladder. This aspect of the syndrome should also be taken into account, therefore, when developing therapeutic strategies.

1.5 A Rational Approach to Management

Do people with IBS need drug therapy? This is a serious question that deserves a serious answer, since it has been suggested that as IBS is so common, possibly affecting up to 1 in 5 of the adult population, it might be regarded as part of the spectrum of normality. Many patients have mild symptoms on an intermittent basis and neither request nor need drug treatment, while others can be incapacitated with persistent symptoms and seek medical advice with a view to permanent cure. Drugs commonly form part of the management strategy for these individuals but this may need to be accompanied by dietary and other lifestyle changes.

2. Current Approaches to Treatment

Dietary and drug therapy for IBS can be considered in 2 categories: (i) treatments that are aimed predominantly at the gut and based on specific, dominant symptoms, so-called end-organ therapy;

Table III. Current approaches to the management of irritable bowel syndrome

General
Explanation of mechanisms of symptom production
Description of brain-gut axis
Reassurance
End-organ therapy
Exclusion diet
Dietary supplements
wheat bran
soluble fibre [psyllium (ispaghula husk)]
Antidiarrhoeal agents
loperamide
diphenoxylate
Antispasmodic agents
scopolamine (hyoscine) butylbromide
mebeverine
dicycloverine (dicyclomine)
dimetropium bromide
pinaverium bromide
Central therapy
Antidepressants
Anxiolytics
Cognitive therapy, psychotherapy and hypnotherapy

and (ii) treatment that is aimed at relieving an associated affective disorder and the use of drugs to modify pain pathways in the CNS, namely central therapy.[1]

2.1. End-Organ Therapy

Standard agents that are considered to act locally in the gut are shown in table III. Fibre preparations are usually restricted to those IBS patients in whom constipation is the major symptom. Recent work indicates that wheat bran can exacerbate abdominal pain and bloating, which is less of a problem with the soluble fibre supplements such as psyllium (ispaghula husk).[13] When bowel frequency is the major symptom, antidiarrhoeal agents such as diphenoxylate or loperamide can be helpful. Anecdotally, tricyclic antidepressants are also reported to reduce bowel frequency – possibly because of their anticholinergic effect, although this has not been examined systematically in a randomised trial.

Traditionally, pain is treated with drugs that reduce gut spasm, such as anticholinergics and smooth muscle relaxants. Klein[2] heavily criticised the trials performed with this class of drug before 1988 and concluded from the available studies that there was 'no convincing evidence that anti-spasmodic agents are of value'. Since his review, further studies have been performed, and Poynard et al.[14] subjected 26 of these studies which fulfilled predetermined inclusion criteria to a meta-analysis using the methods of Sacks et al.[15] They concluded from this overview that 5 drugs (cimetropium bromide, pinaverium bromide, trimebutine, octilium bromide and mebeverine) had clinical efficacy in IBS. The smooth muscle relaxants significantly improved pain and overall well-being although they had no effect on abdominal distension.

2.2 Central Therapy

Central therapy has been considered to be a reasonable approach to treating some patients with IBS because of the associated affective disorder in some of these patients who seek medical advice, and also because of the well recognised disturbance of bowel habit that occurs in individuals with affective disorder (notably constipation in depressed patients). The early clinical trials of antidepressants in IBS, however, produced inconsistent results although the design and analysis of these studies have been severely criticised.[2] Antidepressants, however, are clearly effective in depression and there would be no reason to believe that depressed patients with IBS would not benefit from their use.

The effects of antidepressant drugs on pain threshold are well recognised, particularly for the tricyclic antidepressants, and many physicians therefore consider treatment with an antidepressant when pain is an overriding component of the syndrome. Recent work has confirmed that antidepressants affect gut transit and motility, the tricyclics tending to slow gut transit while the specific serotonin reuptake inhibitors such as paroxetine tend to produce more rapid transit, particularly in the small

intestine.[16,17] These observations might be taken into account when considering the use of these agents in IBS patients with depression or pain.

Some patients are disinclined to take centrally active drugs for IBS and it should not be forgotten that clinical trials have shown the therapeutic efficacy of psychotherapy, cognitive therapy and hypnotherapy in this disorder.[18-20] It would be impractical to believe that these treatments would be available to all patients with IBS, although the value of counselling following a diagnostic interview should not be overlooked and would be regarded as routine by many practising clinicians.

3. New Drugs for Irritable Bowel Syndrome

This section considers new agents that have been developed specifically for the treatment of IBS, and established drugs which have found a new indication. Although the search continues for a single agent that will treat all of the symptoms of IBS, this may, in the light of what has been discussed in section 1 (above) with respect to the divergent symptomatology and pathophysiology, be over-ambitious.

3.1 End-Organ Therapy

This section considers drugs in 2 categories, namely those that predominantly modify gastrointestinal transit (which are aimed at the treatment of bowel frequency and constipation), and those whose prime function is to modify visceral sensation and to treat abdominal pain. However, before considering these agents it seems appropriate to consider the current status of dietary manipulation and dietary supplements in the management of IBS, an approach which is still extremely popular and highly favoured by patients.

3.1.1 Diet, Food Intolerance and Allergy

Food intolerance has been considered to be a factor in symptom production in IBS for many decades. There is, however, a great difference between 'perceived food intolerance' and food intolerance that can be confirmed by double-blind, placebo-controlled challenge. In a recent study, perceived food intolerance was common in the general population at about 20% although only 1 in 5 of those individuals with perceived food intolerance could be confirmed by a controlled challenge.[21] This observation, together with the known high placebo response rate in IBS, means that a healthy scepticism should be retained regarding dietary intervention.

Nanda et al.,[22] however, completed an exclusion diet (exclusion of dairy products, grains, citrus fruits, potatoes, tea, coffee, alcohol, additives and preservatives) and found that 48.2% of patients improved symptomatically. Of the responders, 81.3% were able to identify one or more food intolerances which were confirmed on subsequent challenge. However, the challenge was neither placebo-controlled nor double-blind. This study certainly suggests that some patients can feel better by excluding certain foods from their diet, although whether this has any direct relationship to the aetiopathogenesis of the condition remains to be established.

Dietary supplements have had some popularity in IBS, bran being, until recently, the favourite despite the appearance in the literature of several reasonable, well controlled studies that showed bran was not superior to placebo. Recent work has confirmed unequivocally that bran has no role as a panacea in IBS and in a recent study appeared to make 55% of patients worse.[13] The use of proprietary psyllium fibre preparations improved symptoms in 39% of patients, with only 22% feeling worse. This study indicates that bran should not be advocated routinely in IBS and possibly only used when constipation is a major feature. If, after a short trial, the patient deteriorates or is no better, then it would seem reasonable to give a therapeutic trial of a commercially available soluble fibre preparation.

Compared with food intolerance, food allergy is rare. An open study, however, did suggest that individuals in whom skin prick tests gave positive results to a variety of food antigens were more likely to respond symptomatically to the mast cell

stabilising drug sodium cromoglycate than individuals who tested negatively.[23] The same group then went on to perform a large, multicentre, randomised study comparing sodium cromoglycate with an elemental diet during a 1-month period; 67 and 60% of patients treated with sodium cromoglycate and elemental diet, respectively, improved symptomatically.[24] Unfortunately, there was no placebo control and it is difficult to be certain that these findings do not represent a placebo response. However, symptomatic improvement was significantly greater in skin prick test positive individuals. Further evaluation is required before sodium cromoglycate can be routinely recommended for the treatment of diarrhoea-predominant IBS.

3.1.2 Drugs That Modify Gastrointestinal Transit

Antidiarrhoeal Agents

Antidiarrhoeals such as loperamide, diphenoxylate and codeine phosphate are commonly used to control bowel frequency in IBS. Previous studies of loperamide in IBS have been criticised because they failed to demonstrate a global improvement in symptoms, although it was acknowledged that significant symptomatic benefits were achieved with respect to bowel frequency.[2] For patients in whom bowel frequency is a major symptom, treatment to control such frequency would seem to be a reasonable objective to achieve. In addition, for the reasons stated above (section 1.1) it may be unreasonable to expect any single end-organ approach to achieve the global improvement that all agree is ideal.

A recent double-blind, placebo-controlled trial of loperamide in an unselected group of IBS patients reduced stool frequency by 36%, which was significantly greater than results obtained from placebo.[25] In addition, loperamide also improved stool consistency and reduced pain intensity. The study can be criticised, however, in that only mean values were presented, without ranges or confidence intervals, and the numbers of patients in the loperamide and placebo groups were small (35 and 34, respectively). A more focused study on diarrhoea-predominant IBS might be more informative.

Prokinetic Agents

It is reasonable to propose that some patients with IBS, particularly those with constipation and bloating, might benefit from a prokinetic agent. The only studies with the dopamine antagonist domperidone provided largely negative results. However, preliminary studies indicate that cisapride accelerates gastrointestinal transit in constipation-predominant IBS and that it is of benefit symptomatically in this group of patients. However, a recent double-blind, placebo-controlled trial of cisapride 5 to 10mg 3 times daily for 12 weeks failed to produce improvement in abdominal pain, constipation or abdominal bloating compared with the placebo group.[26] Cisapride would therefore not appear to have a role in the treatment of this group of patients.

The opiate antagonist naloxone accelerates colonic transit, presumably by inhibiting the actions of endogenous opioids. Nalmefene glucuronide is a synthetic opioid antagonist which has been subjected to open-label evaluation in 10 patients with constipation-predominant IBS.[27] Nalmefene decreased transit time and increased stool frequency but appeared not to affect abdominal pain. Further evaluation of this agent in randomised controlled trials is awaited before this drug can be recommended in IBS.

Bulking agents such as wheat bran and soluble fibre are known to accelerate intestinal transit. Polycarbophil calcium, a nondigestible bulking agent, has recently been compared with placebo in 23 IBS patients for 6 months in a randomised, double-blind, crossover study.[28] Overall, 71% of patients chose polycarbophil calcium rather than placebo for symptom relief. Polycarbophil calcium was significantly better than placebo in relieving constipation, alternating diarrhoea and constipation, pain and bloating. However, this was a small study and the findings require confirmation in a larger randomised, controlled trial.

3.1.3 Drugs That Modify Visceral Sensation

Evidence has increased during the past 20 years that visceral hypersensitivity is an important component of a number of functional abdominal disor-

ondansetron reduced the pain response induced by distending the rat duodenum, and granisetron but not alosetron or ondansetron has been shown to reduce cholera toxin–induced intestinal secretion.

5-HT_3 receptor antagonists have been shown to retard colonic transit in addition to their effects on visceral sensation and have therefore been subjected to pilot evaluation in diarrhoea-predominant IBS. A preliminary study has indicated that ondansetron reduces bowel frequency and improves stool consistency in diarrhoea-predominant IBS but did not significantly reduce abdominal pain.[34] 5-HT_4 receptors are also widely distributed throughout the gastrointestinal tract and are thought to be involved in controlling aspects of function. The specific 5-HT_4 antagonist SB-207266A has been shown to prolong orocaecal transit time and tended to reduce rectal sensitivity in diarrhoea-predominant IBS patients.[35] Further studies are required to evaluate the effects of 5-HT antagonists in IBS.

Somatostatin and Somatostatin Analogues

Somatostatin and its analogues are known to have analgesic effects on somatic and visceral pain. Intrathecal and epidural somatostatin has been shown to relieve pain after major abdominal surgery and in patients with advanced malignancy.[36-38] Extensive work in animal models has confirmed its antinociceptive properties. Somatostatin immunoreactivity is found in dorsal route ganglia and nerves in the dorsal horn of the spinal cord. It is thought that endogenous release of somatostatin modulates neural transmission in the spinal cord by depressing the excitability of neurons in the dorsal horn, possibly via inhibitory effects on N-type calcium channels. The antinociceptive effects of somatostatin are generally not inhibited by the opiate receptor antagonist naloxone, indicating that the former is not operating through opiate pathways.

The somatostatin analogue octreotide has many effects on gastrointestinal function, notably reduction of gastrointestinal secretion and retardation of gastrointestinal transit. Octreotide has been shown to reduce mouth-to-caecum transit time in healthy controls and patients with diarrhoea-predominant IBS by a factor of 2.[39] A single case report also suggests that octreotide may have symptomatic benefits in IBS.[40] More recently, the effect of octreotide on rectal sensation in healthy volunteers has been evaluated. In a double-blind, placebo-controlled study, octreotide 100μg subcutaneously increased sensation threshold and maximum tolerated volume while having no effect on thermal or electrical cutaneous stimulation, indicating that octreotide has selectivity for visceral afferent pathways.[41] Although long term treatment with a somatostatin analogue cannot be recommended for IBS, further studies are clearly indicated to establish whether this general approach can be used in the future.

Antidepressants

For many years antidepressant drugs have been used to treat the associated affective disorder in IBS. They have been used on the basis of studies in other disciplines that indicate that these agents, particularly the tricyclic antidepressants, are effective treatments for chronic pain. Recent systematic reviews of randomised trials clearly indicate that tricyclic antidepressants are effective treatments for postherpetic neuralgia, facial pain and painful diabetic neuropathy.[42] The analgesic effect of antidepressants can be achieved at lower doses than those used to treat depression, the onset of action of action occurring before any effect on mood is evident (1 to 7 days), and this effect is not dependent on a change in mood.

There is now a broad choice of antidepressants but there is no evidence that the newer selective serotonin reuptake inhibitors (SSRIs) are any more effective than the tricyclic antidepressants such as amitriptyline.[43] Randomised, controlled trial evidence of the efficacy of antidepressants in IBS is limited but until better evidence is available it would seem reasonable to start with amitriptyline 10 to 25mg at night, increasing gradually at weekly intervals to a maximum of 150mg at night. If patients are intolerant of amitriptyline then it would be reasonable to try one of the newer antidepressants such as an SSRI.

As mentioned above (section 2.2), it may be worth considering our own observations on the effect of antidepressants on gastrointestinal transit. For patients with diarrhoea-predominant IBS we would favour a tricyclic drug, whereas an individual with constipation might fare better with an SSRI.[16,17]

3.1.4 Drugs With Uncertain Mode of Action

Leuprorelin (Leuprolide)

This nonapeptide is an analogue agonist of gonadotrophin-releasing hormone (GnRH). GnRH is a decapeptide produced in the neurosecretory cells of the median basal eminence of the hypothalamus and secreted into the hypothalamic pituitary portal circulation to initiate secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH).[44] FSH stimulates the growth of ovarian follicles in women and spermatogenesis in men. LH promotes ovulation and corpus luteum formation in women and testosterone secretion in men. If GnRH is administered continuously, LH and FSH levels are suppressed by the phenomenon known as 'down-modulation'. This ultimately leads to a dramatic reduction in circulating sex hormone concentrations. Leuprorelin has 15 times the potency of GnRH and when administered continuously suppresses sex hormone levels even more efficiently than GnRH.

Mathias et al.[45] chose to trial leuprorelin on the basis that IBS is more common in women and that IBS symptoms are more troublesome in the postovulatory phase of the menstrual cycle. The relaxant effects of progesterone on smooth muscle have been postulated to be a possible explanation for these observations.[46] The hypothesis those authors tested, therefore, was that suppression of ovulation and menstruation will improve IBS symptoms.

Mathias and colleagues[45] evaluated the effect of leuprorelin in a double-blind, placebo-controlled study in patients with IBS. They also assessed duodenal jejunal motility by manometry and mouth-to-caecum transit time. Symptom scores for nausea, vomiting, bloating, abdominal pain and early satiety and overall symptoms all improved in comparison with placebo. The manometric studies were apparently abnormal in all patients but in none of the controls; the report is unclear, however, as to the composition of the control group and whether it was comparable with patients with IBS. The symptom scores were also difficult to interpret since only median values were given, without ranges or confidence intervals. There were also problems with the design of the study in that the women who received leuprorelin experienced suppression of menstruation and it would have been immediately obvious to these individuals that they had received the active drug. Efforts were made, however, to keep the symptom assessors 'blind'.

28 patients from the placebo-controlled study were then entered into an open-label study for a further 40 weeks.[47] Again, symptomatic improvement appeared to continue. The authors also report anecdotal evidence of experience in treating 10 men with IBS and report a favourable outcome. However, men were less inclined to accept this treatment because of the associated impotence. Despite these apparently favourable preliminary results, leuprorelin would not be a drug that the practitioner would immediately turn to for treating patients with even moderately severe IBS.

Cholecystokinin (CCK) Antagonists

CCK is released in response to meals, particularly fatty meals. CCK delays gastric emptying, accelerates small bowel transit and stimulates colonic smooth muscle. The CCK antagonist loxiglumide failed to alter gastric emptying rate or small bowel transit but reduced colonic transit from 30 hours to about 12 hours.[48] A pilot study has indicated that loxiglumide may be effective in IBS[49] but the results of an ongoing multicentre, randomised, controlled trial are awaited.

3.2 Central Therapy

3.2.1 Antidepressants

There would seem little doubt that depressed patients with IBS should be offered a trial of an antidepressant, as this may not only elevate mood but also help bowel symptoms. A case for using an antidepressant to control visceral pain has been

made above (section 3.1.3), accepting that the evidence in IBS is far from robust. However, in the absence of effective therapy for pain, a therapeutic trial would seem worthwhile.

3.2.2 Anxiolytics

Early studies of the use of anxiolytics either alone or in combination did not produce convincing evidence of efficacy in IBS, largely because of poor study design.[2] This class of drug is no longer widely used in IBS, presumably because of its lack of clinical efficacy and the concerns about benzodiazepine dependence. However, Capurso et al.[50] compared diazepam 2mg 3 times daily with the smooth muscle relaxant octylonium bromide 40mg 3 times daily and a combination of the two. The trial was randomised but not blinded and there was no placebo control, although there was an initial 15-day washout period with placebo. Patients were treated during a 3-month period during which time abdominal symptoms and anxiety were assessed. Combination therapy with octylonium bromide and diazepam had the greatest effect on abdominal symptoms and on the self-rating anxiety scale. Octylonium bromide was more effective than diazepam alone in reducing the intensity of the abdominal pain. Although the study again raises the possibility of using an anxiolytic in IBS, concerns about long term use and drug dependence must outweigh any small short term benefits that might accrue. If anxiety is a major component then it is probably safer to use an antidepressant with additional sedative activity.

4. Conclusions

IBS is a consortium of varied symptoms which presents a major challenge for those seeking single agent therapy. Drugs that modify intestinal transit can be of value in the management of the symptoms of disordered defaecation (antidiarrhoels, prokinetics), although the focus for the immediate future is mainly on drugs that reduce hyperalgesia (kappa opioid agonists, 5-HT_3 amd 5-HT_4 antagonists, antidepressants). Further work is required to explore the links between nociception and smooth muscle dysfunction in the gut.

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